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(54) Title: IONTOPHORETIC DELIVERY OF ROTIGOTINE FOR THE TREATMENT OF PARKINSON'S DISEASE

(57) Abstract: By using a composition comprising rotigotine and at least one chloride salt in a concentration of 1 to 140 mmol/l, the composition having a pH of 4 to 6.5 in a iontophoretic device for the treatment of Parkinson's disease, it became possible to obtain a rotigotine flux across the human stratum corneum which was higher than the one previously obtained with conventional passive diffusion systems.

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Iontophoretic Delivery of Rotigotine for the Treatment of Parkinson's Disease

Description

Field of the Invention

The present invention relates to an effective method for treating or alleviating symptoms of Parkinson's disease, which uses iontophoretic delivery of the dopamine receptor agonist rotigotine (INN).

Technical Background

Parkinson's disease is believed to be primarily caused by the degeneration of dopaminergic neurons in the substantia nigra. This, in effect, results in loss of tonic dopamine secretion and dopamine-related modulation of neuronal activity in the caudate nucleus, and thus in a deficiency of dopamine in certain brain regions. The resulting imbalance of neurotransmitters acetylcholine and dopamine eventually results in disease related symptoms. Although usually regarded as a motor system disorder, Parkinson's disease is now considered to be a more complex disorder that involves both motor and nonmotor systems. This debilitating disease is characterized by major clinical features including tremor, bradykinesia, rigidity, dyskinesia, gait disturbances, and speech disorders. In some patients, dementia may accompany these symptoms. Involvement of the autonomic nerve system may produce orthostatic hypotension, paroxysmal flushing, problems with thermal regulation, constipation, and loss of bladder and sphincter control. Psychological disorders such as loss of motivation and depression may also accompany Parkinson's disease.

Parkinson's disease is primarily a disease of middle age and beyond, and it affects both men and women equally. The highest rate of occurrence of Parkinson's disease is in the age group over 70 years old, where Parkinson's disease exists in 1.5 to 2.5% of that population. The mean age at onset is between 58 and 62 years of age, and most patients develop Parkinson's disease between the ages of 50 and 79. There are approximately 800,000 people in the United States alone with Parkinson's disease.

Early motor deficits of Parkinson's disease can be traced to incipient degeneration of nigral dopamine-releasing cells. This neuronal degeneration produces a defect in the dopaminergic pathway that connects the substantia nigra to the striatum. As the disease progresses, refractory motor, autonomic, and mental abnormalities may develop, which implies that there is progressive degeneration of striatal receptor mechanisms.

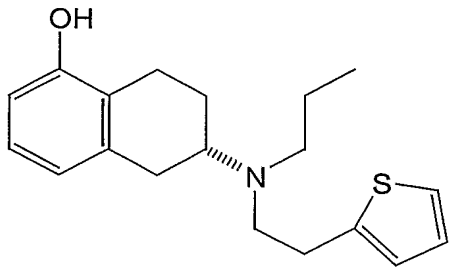
The clinical diagnosis of Parkinson's disease is based on the presence of characteristic physical signs. The disease is known to be gradual in onset, slowly progressive, and variable in clinical manifestation. Evidence suggests that the striatal dopamine content declines to 20% below levels found in age-matched controls before symptoms occur.

Treatment of Parkinson's disease has been attempted with, inter alia, L-dopa (levodopa), which still is the gold standard for the therapy of Parkinson's disease. Levodopa passes the blood-brain barrier as a precursor for dopamine and is then converted into dopamine in the brain. L-dopa improves the symptoms of Parkinson's disease but may cause severe side effects. Moreover, the drug tends to lose its effectiveness after the first two to three years of treatment. After five to six years, only 25% to 50% of patients maintain improvement.

Furthermore a major drawback of currently utilized therapies for Parkinson's disease is the eventual manifestation of the "fluctuation syndrome", resulting in "all-or-none" conditions characterized by alternating "on" periods of mobility with dyskinesias and "off" periods with hypokinesia or akinesia. Patients who display unpredictable or erratic "on-off" phenomena with oral anti-Parkinson therapy have a predictable beneficial response to i.v. administration of L-dopa and other dopamine agonists, suggesting that fluctuations in plasma concentrations of drug are responsible for the "on-off" phenomena. The frequency of "on-off" fluctuations has also been improved by continuous infusions of the dopamine receptor agonists apomorphine and lisuride. However, this mode of administration is inconvenient. Therefore, other modes of administration providing a more constant plasma level, such as topical administration, are beneficial and have been suggested in the past.

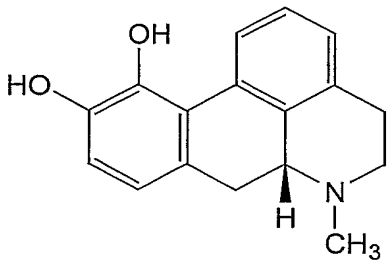
As mentioned above, one treatment approach for Parkinson's disease involves dopamine receptor agonists. Dopamine receptor agonists (sometimes also referred to as dopamine agonists) are substances which, while structurally different from dopamine, bind to different subtypes of dopamine receptors and trigger an effect which is comparable to that of dopamine. Due to the reduced side-effects, it is advantageous when the substances selectively bind to a sub-group of dopamine receptors, i.e. the D2 receptors.

One dopamine receptor agonist which has been used to treat the symptoms of Parkinson's disease is rotigotine. It has mostly been tested in the form of its hydrochloride. Rotigotine is the International Non-Proprietary Name (INN) of the compound (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol having the structure shown below



It has before been known to administrate rotigotine by passive transdermal therapeutic systems (TTS). Such passive transdermal therapeutic systems for the administration of rotigotine have been described for example in WO 94/07568 and WO 99/49852. However, the rotigotine flux obtained with these passive transdermal therapeutic systems is not necessarily sufficient for all patients.

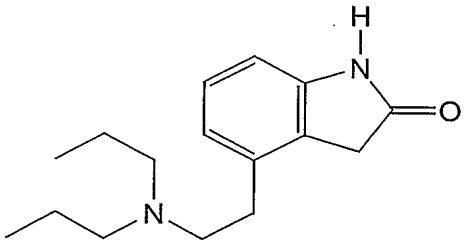
Another dopamine agonist which has been used in the treatment of Parkinson's disease is R-apomorphine. R-apomorphine is the International Non-Proprietary Name (INN) of the compound (R)-5,6,6a,7-tetrahydro-6-methyl-4H-dibenzoquinoline-11,12-diol having the structure shown below



Several approaches to develop a system for iontophoretic administration of R-apomorphine have previously been described (see for example R. van der Geest, M. Danhof, H.E. Boddé "Iontophoretic Delivery of Apomorphine: *In Vitro* Optimization and Validation", Pharm. Res. (1997), 14, 1797-1802; M. Danhof, R. van der Geest, T. van Laar, H.E. Boddé, "An integrated pharmacokinetic-pharmacodynamic approach to optimization of R-apomorphine delivery in Parkinson's disease", Advanced Drug Delivery Reviews (1998), 33, 253-

263). However, in spite of these efforts, only concentrations at the lower end of the therapeutic concentration range of 1.4 to 10.7 ng/ml could be obtained.

A further dopamine antagonist is ropinirole hydrochloride. Ropinirole (INN) is (4-[2-dipropylamina)ethyl]-1,3-dihydro-2H-indol-2-one) having the structure shown below



Although the iontophoretic administration of ropinirole was considered feasible, it was only possible to obtain fluxes at the lower end of the therapeutic range (see A. Luzardo-Alvarez, M. B. Delgado-Charro, J. Blanco-Méndez, "Iontophoretic Delivery of Ropinirole Hydrochloride: Effect of Current Density and Vehicle Formulation", Pharmaceutical Research (2001), 18(12), 1714-1720).

Many patients need concentrations that are significantly higher than the ones feasible using iontophoretic delivery of apomorphine or ropinirole.

In view of the broad range of symptoms of Parkinson's disease and the differing severity, there is a strong demand for a method which allows adjusting the rotigotine flux across the skin and at the same time allows for a constant receptor stimulation of the dopamine receptors of Parkinson patients. Preferably such a system should also allow for rotigotine fluxes higher than the ones achieved by passive transdermal delivery systems.

In view of the discouraging experiences with the iontophoretic delivery of apomorphine, it has been surprising that iontophoretic delivery of rotigotine could provide plasma levels of rotigotine which are not only higher than the ones of conventional passive diffusion systems but are actually in a range that allows for the delivery of pharmaceutically effective drug dosages. The results obtained by using this invention allow for a reasonable expectation that an effective treatment of Parkinson's disease can be provided. It should be understood that the term "treatment" in the context of this application is meant to designate a treatment or alleviation of the symptoms of Parkinson's disease, rather than a real causative treatment leading to a complete cure.

Summary of the Invention

The present invention provides the use of a composition comprising rotigotine and at least one chloride salt in a concentration of 1 to 140 mmol/l, the composition having a pH of 4 to 6.5 for the preparation of a iontophoretic device for the treatment of Parkinson's disease.

Iontophoresis is the introduction of various ions into the skin by means of electricity. If compared to passive transdermal delivery, iontophoresis provides for several advantages which are useful in the treatment of Parkinson's disease:

- it allows programming of the flux at the required therapeutic rate by adjusting the electric current, and

- it permits a rapid start or termination of administration of the medication, if needed, by simply turning the iontophoretic delivery system on or off.

As the iontophoretic flux is influenced by several parameters, it is crucial for achieving an optimal flux to separately optimise these parameters.

Surprisingly, it was found that using a composition having a pH of 4 to 6.5 and comprising rotigotine and at least one chloride salt in a concentration of 1 to 140 mmol/l in the donor chamber of the iontophoretic device, fluxes well within the therapeutic range could be achieved.

By reducing the electrolyte concentration in the donor compartment it was possible to achieve the target iontophoretic flux at lower current density or to increase the transdermal dose per area unit.

During the studies conducted to evaluate the feasibility of iontophoretic delivery of rotigotine, it was found that the solubility of rotigotine decreases when the pH is increased. However, surprisingly it was found that a therapeutically relevant rate was achieved within the pH interval of 4 to 6.5 at very low rotigotine concentrations.

To provide for an optimal flux across human stratum corneum it was also necessary to provide for a sufficient concentration of Cl^- ions for the electrode reaction in the donor phase. However, while maintaining the electrode reaction the addition of chloride salts reduces the solubility of rotigotine. Thus, a concentration of chloride salts of 1 to 140 mmol/l, preferably 50 to 100 mmol/l, more preferably 60 to 80 mmol/l, proved optimal.

The rotigotine concentration may be varied in accordance with the patient's needs and the flux required for obtaining a therapeutic effect in the treatment Parkinson's disease. However, for a optimal performance it is preferably at least 0.5 mg/ml, more preferably 0.5 mg/ml to 3 mg/ml.

All chloride salts which are pharmaceutically acceptable may be employed in the composition of the invention. In a preferred embodiment of the invention the chloride salt is selected from NaCl, triethylammonium chloride and tributylammonium chloride. Triethylammonium chloride and tributylammonium chloride are especially preferred, because they result in higher fluxes of rotigotine.

In an especially preferred embodiment of the invention the composition, which is used as the donor phase of the iontophoretic device, comprises rotigotine in a concentration of 0.5 to 3 mg/ml and at least one of triethylammonium chloride and tributylammonium chloride in a concentration of 60 to 80 mmol/l, the donor phase has a pH of 4.5 to 5.5.

In another aspect the present invention provides a method for the treatment of Parkinson's disease, wherein a iontophoretic device, which comprises a composition comprising rotigotine and at least one chloride salt in a concentration of 1 to 140 mmol/l, the composition having a pH of 4 to 6.5, is applied onto the skin of a patient in need thereof.

Any conventional iontophoretic device may be used in the invention. Such iontophoretic devices are described e.g. in V. Nair, O. Pillai, R. Poduri, R. Panchagnula, "Transdermal Iontophoresis. Part I: Basic Principles and Considerations" Methods Find. Exp. Clin. Pharmacol. (1999), 21(2), 139-151.

The current density employed during iontophoresis may be varied according to the patient's needs and will depend on the iontophoretic device and the composition used. A suitable current may be determined by the attendant physician. In general, a suitable current density will be in the range of preferably 200 to 500 $\mu A/cm^2$.

Example 1

In vitro iontophoretic studies for the administration of rotigotine were carried out with three-chamber flow-through diffusion cells as described by R. van der Geest et al. (R. van der Geest, M. Danhof, H.E. Boddé, "Validation and testing of a new iontophoretic continuous flow through transport cell", J. Control. Release (1998), 51, 85-19). On both sides of the acceptor compartment human stratum corneum (SC) was situated. A dialysis membrane having a 5.000 Da cut-off was used as supporting membrane. The volume of the outer chambers was approximately 2 ml, while the volume of the acceptor compartment was 0.54 ml. The two outer chambers contained the silver plate (anode) or silver/silver chloride (cathode) driver electrons. The donor phase consisted of rotigotine solution buffered with 5 mM citrate buffer (2.1 mM sodium citrate dihydrate and 2.9 mM citric acid).

Using this set-up, a pH in the donor chamber of 5, a current density of 500 $\mu A/cm^2$, a pH in the acceptor chamber of 7.4, a temperature of 20°C and an NaCl concentration in the donor chamber of 70 mmol/l, the flux of rotigotine was measured for different drug concentrations in the donor phase.

Rotigotine conc. (mg/ml) (Donor solution)	**Rotigotine conc. (mM) (Donor solution)**	**Flux (nmol/cm²/h) Rotigotine**
0.5	1.4	22.9
1.0	2.8	30.2
1.4	3.98	53.2

Example 2:

Using a similar procedure as in Example 1 and a concentration of rotigotine of 1.4 mg/ml (3.98 mM), a pH in the donor

chamber of 5, a current density of 500 $\mu A/cm^2$, a pH in the acceptor chamber of 7.4 and a temperature of 20°C, but substituting triethylammonium chloride (TEACl) or tributylammonium chloride (TBACl) for NaCl, the influence of the different cations on the flux was evaluated. The concentration of the chloride salts in the donor solution was 70 mmol/l.

Co-ions source	**Flux ($nmol/cm^2/h$) Rotigotine**
NaCl	53.2
TEACl	72.8
TBACl	62.0

Example 3:

Using a similar procedure and the same parameters as in Example 2, the influence of reducing the pH in the acceptor chamber from 7.4 to 6.2 was evaluated for different chloride salts. The concentration of the chloride salts in the donor solution was 70 mmol/l.

Co-ions source	**Flux ($nmol/cm^2/h$) Rotigotine**
NaCl	58.9
TEACl	43.2
TBACl	76.5

Claims

1. Use of a composition comprising rotigotine and at least one chloride salt in a concentration of 1 to 140 mmol/l, the composition having a pH of 4 to 6.5 for the preparation of a iontophoretic device for the treatment of Parkinson's disease.

2. Use according to claim 1, wherein the concentration of rotigotine is at least 0.5 mg/ml.

3. Use according to any one of claims 1 or 2, wherein the concentration of rotigotine is 0.5 to 3 mg/ml.

4. Use according to any one of claims 1 to 3, wherein the chloride salt is selected from NaCl, triethylammonium chloride and tributylammonium chloride.

5. Use according to claim 4, wherein the chloride salt is triethylammonium chloride or tributylammonium chloride.

6. Use according to any one of claims 1 to 5, wherein the concentration of the chloride salt is 60 to 80 mmol/l.

7. Use according to any one of claims 1 to 6, wherein the composition is used in the donor phase of the iontophoretic device.

8. Use according to any one of claims 1 to 7, wherein the composition in the donor phase of the iontophoretic device comprises rotigotine in a concentration of 0.5 to 3 mg/ml and at least one of triethylammonium chloride and tributylammonium chloride in a concentration of 60 to 80 mmol/l, wherein the pH of the donor phase is 4.5 to 5.5.

9. A method for the treatment of Parkinson's disease characterised by applying a iontophoretic device, which comprises a composition comprising rotigotine and at least one chloride salt in a concentration of 1 to 140 mmol/l, the composition having a pH of 4 to 6.5, onto the skin of a patient in need thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/13111

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/381 A61K47/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE, BIOSIS, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LI G L ET AL: "Iontophoretic delivery of apomorphine in vitro: Physicochemic considerations" PHARMACEUTICAL RESEARCH 2001 UNITED STATES, vol. 18, no. 11, 2001, pages 1509-1513, XP001149891 ISSN: 0724-8741 abstract page 1510, right-hand column, paragraph 2 - paragraph 3 page 1511, left-hand column, paragraph 2 -right-hand column, paragraph 1 page 1511, right-hand column, paragraph 3 -page 1513, left-hand column, paragraph 2 --- -/--	1-9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 April 2004	14/04/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Langer, O

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/13111

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 49852 A (LOHMANN THERAPIE SYST LTS ;MUELLER WALTER (DE); PECK JAMES V (US);) 7 October 1999 (1999-10-07) abstract page 1, paragraph 1 page 2, paragraph 3 -page 3, paragraph 1 page 3, paragraph 4 -page 4, line 2 ---	1-9
Y	DANHOF M ET AL: "An integrated pharmacokinetic-pharmacodynamic approach to optimization of R-apomorphine delivery in Parkinson's disease." ADVANCED DRUG DELIVERY REVIEWS, vol. 33, no. 3, pages 253-263, XP002237909 ISSN: 0169-409X cited in the application abstract page 258, right-hand column, paragraph 2 -page 262, right-hand column, paragraph 2 ---	1-9
Y	US 4 996 226 A (HORN ALAN S) 26 February 1991 (1991-02-26) abstract column 1, line 16 - line 31 column 3, line 25 - line 32 column 9, line 33 - line 42 claim 19 ---	1-9
A	WO 02 15903 A (SANOL ARZNEI SCHWARZ GMBH ;KREIN CLIFF (DE); THELEN MARKUS (DE); G) 28 February 2002 (2002-02-28) abstract page 1, line 18 -page 2, line 31 ---	1-9
A	DAAS DEN I ET AL: "TRANSDERMAL ADMINISTRATION OF THE DOPAMINE AGONIST N-0437 AND SEVEN ESTER PRODRUGS: COMPARISON WITH ORAL ADMINISTRATION IN THE 6-OHDA TURNING MODEL" NAUNYN-SCHMIEDEBERG'S ARCHIVES OF PHARMACOLOGY, SPRINGER, BERLIN, DE, vol. 342, no. 6, December 1990 (1990-12), pages 655-659, XP001062117 ISSN: 0028-1298 abstract figure 1 page 657, right-hand column, last paragraph -page 659, left-hand column, paragraph 2 -----	1-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/13111

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 9 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/13111

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9949852 A	07-10-1999	DE 19814084 A1	14-10-1999
		AT 210973 T	15-01-2002
		AU 746856 B2	02-05-2002
		AU 2934199 A	18-10-1999
		BR 9909313 A	21-11-2000
		CA 2326630 A1	07-10-1999
		CN 1295470 T	16-05-2001
		DE 59900581 D1	31-01-2002
		DK 1033978 T3	15-04-2002
		WO 9949852 A1	07-10-1999
		EP 1033978 A1	13-09-2000
		ES 2170573 T3	01-08-2002
		HK 1031196 A1	10-05-2002
		HU 0101519 A2	28-09-2001
		ID 26646 A	25-01-2001
		JP 2002509878 T	02-04-2002
		NO 20004915 A	08-11-2000
		NZ 507066 A	31-01-2003
		PL 343255 A1	30-07-2001
		PT 1033978 T	28-06-2002
		SI 1033978 T1	31-10-2002
		SK 14462000 A3	09-04-2001
		TR 200002829 T2	22-01-2001
		ZA 200005261 A	22-05-2001
US 4996226 A	26-02-1991	US 4885308 A	05-12-1989
		US 4564628 A	14-01-1986
		US 4657925 A	14-04-1987
		AU 628353 B2	17-09-1992
		AU 3737789 A	12-01-1990
		CA 1338508 C	06-08-1996
		EP 0420871 A1	10-04-1991
		JP 2780834 B2	30-07-1998
		JP 3504972 T	31-10-1991
		KR 145557 B1	17-08-1998
		WO 8912445 A1	28-12-1989
		US 5177112 A	05-01-1993
		US 5268385 A	07-12-1993
		US 5256661 A	26-10-1993
		AU 601961 B2	27-09-1990
		AU 6678286 A	25-06-1987
		EP 0230629 A2	05-08-1987
		EP 0389475 A1	03-10-1990
		JP 62252719 A	04-11-1987
		WO 8912949 A1	28-12-1989
		US 4722933 A	02-02-1988
		US 4743618 A	10-05-1988
WO 0215903 A	28-02-2002	DE 10041479 A1	14-03-2002
		AU 8982001 A	04-03-2002
		CA 2420061 A1	20-02-2003
		WO 0215903 A2	28-02-2002
		EP 1313467 A2	28-05-2003
		US 2003166709 A1	04-09-2003